EXHIBIT 15

IN THE UNITED STATES PATENT OFFICE

Application Serial No. 09/567,451

Our Ref.: PT1830000
CUSTOMER NO. 23607

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Title: CHRONOTHERAPEUTIC DILTIAZEM FORMULATIONS AND THE ADMINISTRATION THEREOF

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Examiner: Amy E. Pulliam

Group Art Unit: 1615

Due Date: August 12, 2002

RESPONSE TO OFFICIAL ACTION
OF FEBRUARY 11, 2002
AMENDMENTS AND REMARKS

August 9, 2002

The Commissioner of Patents
UNITED STATES PATENT OFFICE
2011 South Clark Place
Crystal Plaza 2, Room 1B03
Arlington, Virginia 22202
U.S.A.

Dear Sir:

In response to the outstanding Official Action dated February 11, 2002 and due for response May 11, 2002, Applicant encloses a Request for a three month

extension of time with the fee for a large entity of $920.00 U.S. funds making this response due August 11, 2002. Since August 11, 2002 falls on a Sunday, the due date is extended to Monday, August 12, 2002. If there is any deficiency or surplusage of the fees enclosed for the Extension of Time, please obtain any such deficiency or credit the surplusage to Deposit Account 08-3255 and advise Applicant's Agent.

Please enter the following submissions:

IN THE CLAIMS

Please amend the claims as follows:

1. (Twice Amended) A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem selected from the group consisting of Diltiazem and [including] the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg (as desired) of the form of Diltiazem associated with excipients including a neutral copolymer to provide controlled (sustained) release of the form of Diltiazem for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the form of Diltiazem is adapted to be released after administration over a prolonged period of time and exhibits when given to humans

(i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and

(ii) bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria.

2. (Amended) The controlled release Galenical preparation of claim 1 wherein the higher bioavailability achieved after night administration of the preparation than

morning administration without food exceeds 25% C_{max}, and the neutral copolymer is a neutral acrylic copolymer of ethyl acrylate and methyl methacrylate.

4. (Twice Amended) The controlled-release Galenical preparation of claim 1 wherein the form of Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem (i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 1% and about 15% after 2 hours;
(b) between about 7% and about 35% after 4 hours;
(c) between about 30% and about 58% after 8 hours;
(d) between about 55% and about 80% after 14 hours; and
(e) and in excess of about 75% after 24 hours.

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 1% and about 25% after about 2 hours;
(b) between about 7% and about 45% after about 4 hours;
(c) between about 30% and about 68% after about 8 hours;
(d) in excess of about 75% after about 24 hours.

5. (Twice Amended) The controlled-release Galenical preparation of claim 2 in which the form of Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem (i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;

(b) between about 16% and about 21% after 4 hours;

(c) between about 44% and about 52% after 8 hours;

(d) between about 69% and about 76% after 14 hours; and

(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;

(b) between about 16% and about 30% after 4 hours;

(c) between about 44% and about 62% after 8 hours;

(d) in excess of about 80% after 24 hours.

7. (Amended) The preparation of claim 1, 2, 4, 5 or 6 wherein the form of Diltiazem is in the form of Diltiazem HCl.

48. (Twice Amended) The preparation of claim 17 wherein the wetting agent is selected from:

sugars;

saccharose, mannitol, sorbitol;

lecithins;

C_{12} to C_{20} fatty acid esters of saccarose[, including sucrose stearate];

xylose esters or xylites;

polyoxyethylenic glycerrides;

esters of fatty acids and polyoxyethylene;

sorbitan fatty acid ester;

polyglycides-glycerides and polyglycides-alcohols esters

Metal salts.

52. (Third Amendment) A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem selected from the group consisting of Diltiazem and [including] the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg (as desired) of the form of Diltiazem associated with excipients to provide controlled (sustained) release of the form of Diltiazem for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the form of Diltiazem is adapted to be released after administration over a prolonged period of time and exhibits when given to humans

(i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and

(ii) bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose [(Avicel ph101)]	8 - 9.5
(c)	[Povidone K30] (Polyvinyl Pyrrolidone)	1 - 2
(d)	Sucrose stearate	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3

(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	[Polysorbate 80 (tween)] (Polyoxyethylene Sorbitan Monooleate)	0.01 - 0.025
(j)	Simethicone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing)

64. (Third Amendment) A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem selected from the group consisting of Diltiazem and [including] the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg (as desired) of the form of Diltiazem associated with excipients to provide controlled (sustained) release of the form of Diltiazem for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the form of Diltiazem is adapted to be released after administration over a prolonged period of time and exhibits when given to humans

(i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and

(ii) bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria, in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants,

wherein the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose [(Avicel ph101)]	8 - 9.5
(c)	[Povidone K30] (Polyvinyl Pyrrolidone)	1 - 2
(d)	Sucrose stearate [(crodesta F150)]	7 - 8

(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	[Polysorbate 80 (tween)] (Polyoxyethylene Sorbitan Monooleate)	0.01 - 0.025
(j)	Simethicone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing).

110. (Twice Amended) A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem selected from the group consisting of Diltiazem and [including] the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;

(b) between about 16% and about 21% after 4 hours;

(c) between about 44% and about 52% after 8 hours;

(d) between about 69% and about 76% after 14 hours; and

(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;

(b) between about 16% and about 30% after 4 hours;

(c) between about 44% and about 62% after 8 hours;

(d) in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the wetting agent is selected from:

sugars;

saccharose, mannitol, sorbitol;

lecithins;

C_{12} to C_{20} fatty acid esters of saccarose[, commercialized under the name of sucroesters or under the name of crodesters such as sucrose stearate marketed under the trade name of Crodesta];

xylose esters or xylites;

polyoxyethylenic glycerrides;

esters of fatty acids and polyoxyethylene;

sorbitan fatty acid esters;

polyglycides-glycerides and polyglycides-alcohols esters

Metal salts.

114. (Third Amendment) A controlled-release Galenical preparation of pharmaceutically acceptable <u>form of</u> Diltiazem <u>selected from the group consisting of</u>

Diltiazem and [including] the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;

(b) between about 16% and about 21% after 4 hours;

(c) between about 44% and about 52% after 8 hours;

(d) between about 69% and about 76% after 14 hours; and

(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;

(b) between about 16% and about 30% after 4 hours;

(c) between about 44% and about 62% after 8 hours;

(d) in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, in which the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose	8 - 9.5
(c)	[Povidone K30] (Polyvinyl Pyrrolidone)	1 - 2
(d)	Sucrose stearate	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	[Polysorbate 80 (tween)]	0.01 - 0.025
	(Polyoxyethylene Sorbitan Monooleate)	
(j)	Simethicone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing)

116. (Twice Amended) A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem selected from the group consisting of Diltiazem and [including] the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;

(b) between about 16% and about 21% after 4 hours;

(c) between about 44% and about 52% after 8 hours;

(d) between about 69% and about 76% after 14 hours; and

(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;

(b) between about 16% and about 30% after 4 hours;

(c) between about 44% and about 62% after 8 hours;

(d) in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

118. (Twice Amended) A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem selected from Diltiazem and [including] the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;

(b) between about 16% and about 21% after 4 hours;

(c) between about 44% and about 52% after 8 hours;

(d) between about 69% and about 76% after 14 hours; and

(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;

(b) between about 16% and about 30% after 4 hours;

(c) between about 44% and about 62% after 8 hours;

(d) in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, in which the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

122. (Twice Amended) A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem selected from the group consisting of Diltiazem and [including] the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

126. (Twice Amended) The preparation of claim 122, 123 or 124 wherein the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose [(Avicel ph101)]	8 - 9.5
(c)	[Povidone K30] (Polyvinyl Pyrrolidone)	1 - 2
(d)	Sucrose stearate [(crodesta F150)]	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	[Polysorbate 80 (tween)] (Polyoxyethylene Sorbitan Monooleate)	0.01 - 0.025
(j)	Simethicone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	[Eudragit NE30 D] <u>a neutral acrylic polymer of acrylic acid ethyl ester and</u>	

acrylic acid methyl ester (dry of 30%)	7 - 11
Purified water USP	0 (used for mixing).

No new subject matter has been added.

REMARKS

Claims 1 to 66, 110, 112 to 119, 122 to 128 remain in the Application.

Applicant acknowledges the Examiner's indication of allowable subject matter, namely Claims 114 and Claims 52, 64 and 126 if re-written to overcome 35 U.S.C. §112, second paragraph, rejection and to include all of the limitations of the base claim and any intervening claims. Claims 52 and 64, the Examiner is reminded, are independent claims and therefore there are no other limitations. Claim 126 is dependent on Claim 122, 123 or 124.

Claim Rejections – 35 U.S.C. §112

The Examiner has rejected Claims 48, 52, 64, 110, 114 and 126 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant has amended the claims in order to overcome same. Namely, the phrases "such as" and "including" have been removed and furthermore, trade marks or trade names have been deleted from the claim language in Claims 52, 64, 110, 114 and 126. Therefore, reconsideration of Claims 48, 52, 64, 110, 114 and 126 are respectfully requested.

Claim Rejections 35 U.S.C. §102

The Examiner has rejected Claims 1-41, 43 and 47 under 35 U.S.C. §102(b) as being anticipated by EPA 856 313. Firstly, Applicant respectfully submits nowhere is there found in EPA 856 313 the inclusion of a neutral copolymer. What is found throughout EPA 856 313 is copolymers of acrylic and methacrylic acid esters such as Eudragit RS and Eudragit RL which contain functional groups whereas a neutral copolymer found (in one of Applicant's examples Eudragit NE30D) in Applicant's application is a "neutral copolymer" without any functional groups that form water insoluble films. Nowhere is this found in EPA 856 313. Again, in one of Applicant's examples, Eudragit NE30D generates film coatings of high flexibility even after wetting in an aqueous medium, and furthermore, Eudragit NE30D does not require a plasticizer to generate said film. Eudragit RS and RL normally require a plasticizer. Normally 20% plasticizer must be added to Eudragit RL and RS to obtain films of adequate flexibility. Furthermore, as stated in the application, when the typical formulation disclosed in EPA 856 313 was tested, in one instance the EPA 856 313 formulation failed to reach the desired higher bioavailability when given at night (see Biopharmaceutics & Drug Disposition, Vol. 17, pages 107-115, 1996) (see page 9 of Applicant's application) and also failed to demonstrate better clinical efficacy on hypertension when given at night. See Chronobiology International, January, of Vol. 14(1), pages 71-84 (1997). (See pages 2-3 of Applicant's application.) Applicant respectfully submits that one of the reasons for the unexpected results in Applicant's invention over and above the failures found in the prior art is due to the addition of the neutral copolymer which is not found in the EPA 856 313 reference. Furthermore, when looking at the release characteristics, when one compares release characteristics it is essential that one compares release characteristics in the same medium. Namely, one can compare dissolution rates in potassium chloride and phosphate buffer, however, one cannot compare those dissolution rates in those mediums with dissolution rates in water. The Examiner

has indicated that EPA 856 313 has a dissolution rate of from 0%-35% after 2 hours from 4%-45% after 4 hours, from 30%-75% after 8 hours, from 60%-95% after 13 hours and not less than 85% after 24 hours. This is measured in 0.05 molar potassium chloride at pH 7.0. The dissolution rate in Applicant's claims, namely the buffered medium dissolution rates are not the same, namely the EPA 856 313 reference provides for not less than 85% after 24 hours, whereas Applicant has a lower limit of in excess of 75% after 24 hours in one instance and an excess of 80% after 24 hours in another instance. This is not the same lower limit as found in EPA 856 313, namely not less than 85% after 24 hours. It is wrong to compare dissolution rates when using different dissolution medium. Applicant encloses an article by Bodmeier, R. et al. entitled "The Influence of Buffer Species and Strength on Diltiazem HCl Release from Beads Coated with the Aqueous Cationic Polymer Dispersions, Eudragit RS, RL 30D", attached as **Exhibit "C"**.

Therefore, Applicant respectfully submits EPA 856 313 does not anticipate Applicant's invention as claimed due to the lack of a neutral copolymer in the prior art reference and also due to the lack of the results of a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria. Therefore, reconsideration of Claims 1-41, 43 and 47 under 35 U.S.C. §102(b) as being anticipated by EPA 856 313 is respectfully requested.

<u>Claim Rejection 35 U.S.C. §103</u>

The Examiner has rejected Claims 1-51, 53-66, 110-113, 115-125, 127 and 128 under 35 U.S.C. §103(a) as being unpatentable over EPA 856 313. The Examiner has indicated that in order to overcome this rejection it is necessary for the Applicant to include in the independent composition claims what addition to the composition

render the unexpected results. Applicant respectfully submits that the addition to the composition claim that renders the unexpected results, in one instance the addition of the neutral copolymer, then again in another instance, the neutral acrylic copolymer of ethyl acrylate and methyl methacrylate which is never found in EPA 856 313. Applicant respectfully believes but does not want to be limited to the fact that it is this ingredient in the composition which results in the unexpected results as provided in the claims and throughout the specification and as discussed with the Examiner previously. There is no motivation in EPA 856 313 to include a neutral copolymer in a controlled release galenical preparation of a form of Diltiazem to result in the desired release characteristics as well as a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria. Therefore, reconsideration of Claims 1-51, 53-66, 110-113, 115-125, 1127 and 128 as being rejected under 35 U.S.C. §103(a) over EPA 856 313 is respectfully requested. The articles referred to previously, namely, the Biopharmaceutics & Drug Disposition article and the Chronobiology International article provide that the formulation as taught by EPA 856 313 failed to reach the desired higher bioavailability when given at night and failed to demonstrate better clinical efficacy on hypertension when given at night. This clearly provides prior failure by others in a chronotherapeutic diltiazem formulation, thus making the claims unobvious (See *Hughes Tool Co. v. Dresser Industries*, 816 F.2d 1549, 2 U.S.P.W. 2d 1396 (Fed. Cir. 1987); *In re Dow Chemical Co.*, 837 F.2d 469, 5 U.S.P.Q. 2d 1529 (Fed. Cir. 1988); *Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 16 .S.P.Q. 2d 1923 (Fed. Cir. 1990); *Applied Materials, Inc. v. Advanced Semiconductor Materials America, Inc.*, 98 F.3d 1563, 1568, 40 U.S.P.Q. 2d 1481, 1486 (Fed. Cir. 1996)). Applicant's invention, on the other hand, succeeds on at least both counts and thus this unexpected result and success, which Applicant believes results from the addition of a neutral copolymer, is

unobvious and therefore inventive over the prior art. Therefore, reconsideration is respectfully requested.

103 Rejection

The Examiner has rejected Claims 1-51, 53-66, 110-113, 115-125, 127 and 128 under 35 U.S.C. §103(a) as being unpatentable over WO 93/00093. In this regard, Applicant respectfully submits WO 93/00093 does not disclose a dissolution range suitable for nighttime administration thus not providing a formulation as per Applicant's invention. The only examples that are remotely similar, if that, to Applicant's invention is that found firstly in Example 3 with a 62% dissolution at 8 hours, and then Example 4 with a Tmax at 8 hours. There is not one example found in WO 93/00093 which is close to the Tmax of between 10 and 15 hours after administration and dissolution in water at 8 hours to be between about 30% and about 58% in one instance. These ranges are never disclosed or found in WO 93/00093. All the dissolutions in water of WO 93/00093 vary from Applicant's invention. For example, at page 4, lines 33 and 34 there is provided after 8 hours between 50% and about 90% wherein Applicant provides between about 30% and about 58%. Applicant's dissolution rates are the dissolution rates required in order to provide for a suitable nighttime administration resulting in higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria. As explained in the application, in order to optimally deliver the drug in the morning, the peak plasma level should occur between 6 a.m. and 12 noon when the drug is given at night between 7 p.m. and 10 p.m. The dissolutions provided at 8 hours in water in WO 93/00093 does not provide for this and therefore cannot teach Applicant's invention. The rate of release disclosed by WO 93/00093 is too fast to allow the drug to exhibit a higher bioavailability when given at night compared to

the same does given in the morning in the fasting state. Therefore, there clearly cannot be any teaching of Applicant's invention found in WO 93/00093. Applicant previously indicated to the Examiner that the degree of fluctuation (i.e. the peak to trough variance for WO 93/00093) is much larger than that of Applicant's formulation. Applicant provided evidence to reinforce this statement. The Examiner indicated that the data regarding Tiazac was concerning a 240 mg formulation and the data regarding Applicant's formulation was based on a 300 mg formulation and that the comparison was not persuasive and the rejection was maintained. Applicant respectfully submits that as can be seen previously found in Schedule 4 of the previous response, page 22, the degree of fluctuation of three different formulations, namely 120 mg, 240 mg and 300 mg formulations remained constant and that the degree of fluctuation based on Cmin of the WO 93/00093, as found in Example 4 of same, leads to a percentage fluctuation swing of 139%. The degree of fluctuation in the prior art is much higher than what is found in the present invention. Therefore, although the Examiner indicates that 240 mg cannot be compared to 300 mg, Applicant has shown that 240 mg is compared not only to a 300 mg formulation, but also a 240 mg and a 120 mg formulation as found in Schedule 4, page 22. Therefore, reconsideration is respectfully requested in the rejection of the claims over WO 93/00093. Furthermore, Figure 8 of Applicant's application provided the Examiner with clear differences in dissolution and concentration level of Applicant's formulation at 240 mg and the Tiazac formulation at 240 mg which is the formulation that corresponds to WO 93/00093.

Furthermore, Applicant provides the Examiner with an article dated May 17, 2002 where researchers at the 17th Annual Scientific Meeting of the American Society of Hypertension presented that a formulation based on the claims of the present application showed that all nighttime dosages of graded-release diltiazem produced dose related reductions in trough diastolic and systolic blood pressure demonstrating that the agent maintains its anti-hypertensive effect for a complete 24

hour period. Researchers highlighted data showing the 360 mg nighttime dose lowered mean diastolic blood pressure between 6 a.m. and noon by an additional 3.3 mm of mercury and mean systolic blood pressure by an additional 5.3 mm of mercury when compared with the equivalent morning dose. Lowering mean systolic blood pressure is especially significant since recent data show systolic blood pressure may be a better predictor than diastolic blood pressure of coronary artery disease, heart failure, stroke and death. Dr. Stephen Glasser, lead study author and professor of epidemiology at the University of Minnesota, School of Public Health, indicated that the improved efficacy of the evening dose during the high risk morning hours demonstrates the ability of this new formulation to synchronize it with circadian rhythms. Their findings reinforce that nighttime dosing of chronotherapeutic agents is an important option to maximize blood pressure control when patients are at greater risk for cardiovascular events.

Therefore, not only has Applicant provided data to support the inventiveness of the claimed subject matter, but also medical and scientific personnel are now reporting on the overwhelming results of Applicant's formulation thus provide better and efficient modes of combating heart disease, stroke, heart failure and death. Thus, there is also found praise by experts in the field which again results in a conclusion of non-obviousness (see *Panduit Corp. v. Dennison Mfg. Co.*, 774 F.2d 1082, 227 U.S.P.Q. 337 (Fed. Cir. 1985); *Symbol Technologies Inc. v. Opticon Inc.*, 935 F.2d 1569, 1578, 19 U.S.P.Q. 2d 1241, 1248 (Fed. Cir. 1991); *Ryko Manufacturing Co. v. Nu-Star Inc.*, 950 F.2d 714, 21 U.S.P.Q. 2d 1053 (Fed. Cir. 1991); *Applied Materials, Inc. v. Advanced Semiconductor Materials America, Inc.*, 98 F.3d 1563, 1568, 40 U.S.P.Q. 2d 1481, 1486 (Fed. Cir. 1996)).

Although the Examiner has taken the position that all of the elements of Applicant's claims are found in the prior art, which Applicant denies, Applicant would like to provide the following case law which supports that an invention is not

obvious where old or well-known elements solve a different problem (see Lindermann Maschinenfabrik GmbH v. American Hoist and Derrick Company, 730 F.2d, 1452, 221 USPQ 481 (Fed. Cir. 1984) which provides that an invention that is a combination of old elements will be non-obvious if the old elements typically deal with different problems.) Specifically, the Federal Court stated "nothing in the references alone or together suggest a claimed invention as a solution to the problem of crushing rigidly massive scrap". There was nothing whatever of record therefore to support the District Court's statement that the claimed machine possessed "another known procedure operating in a known manner to produce a known result"... "That the claimed invention may employ known principals does not itself establish that the invention would have been obvious". Clearly if all the elements were found in the prior art, which Applicant denies, there is no teaching of the elements of Applicant's invention to solve a different problem, namely to solve a problem of achieving a chronotherapeutic formulation having the characteristics outlined in Applicant's claims. Furthermore, although the Examiner states that it would have been obvious in light of the prior art to one of ordinary skill in the art at the time of the invention to create a controlled release formulation of diltiazem in order to achieve the desired rate of release, Applicant respectfully submits as per ex parte Obukowicz, 27 USPQ 2d, 1063 (B.P.A.I. 1992) that the invention is not obvious where the prior art only provides invitation to explore, even though the prior art could theoretically explain the invention, although Applicant denies that there is any invitation to explore and thus arrive at Applicant's invention, this is not the case. None of the references alone or combined result in Applicant's claimed invention. Furthermore, none of the references along or combined address the problem of providing a chronotherapeutic formulation resulting in a more effective treatment of heart disease and associated conditions with the solution that Applicant has provided in this application. Thus, the prior art did not appreciate the problem in one instance and in another instance did not provide a solution to the problem as per Applicant's invention. Furthermore, Applicant also provides the article of May 17,

2002, a copy of which is enclosed as **Exhibit "D,"** not only to show the praise of experts but also as per In re Zenitz, 333 F.2d 924, 142, USPQ 158 (C.C.P.A. 1964) that Applicant's may use unexpected benefits discovered after the application is filed to show non-obviousness. This is the case where the medical doctors found the superiority of Applicant's invention.

Therefore, in light of the above submission, Applicant respectfully submits that the claims are now all in condition for allowance and that the claimed subject matter is not anticipated nor obviated by the prior art references and Applicant respectfully requests allowance of the case by the Examiner.

On a side note, after speaking with the inventors, Applicant decided to file a response firstly with the arguments mentioned and allow the Examiner to review same at which point Applicant's agent will contact the Examiner to arrange an interview if required.

Furthermore, should the Examiner require any affidavit evidence to support Applicant's submissions, the Examiner is asked to notify the Applicant of same and Applicant's agent will attend to same.

Attached hereto as **Exhibit A** is a marked-up version of the changes made to the claims by the present amendment. Exhibit A is entitled "EXHIBIT A - CLAIMS WITH MARKINGS TO SHOW CHANGES".

Attached hereto as **Exhibit B** is a clean set of all pending claims following entry of this amendment. Exhibit B is entitled: "EXHIBIT B - CLEAN SET OF ALL PENDING CLAIMS FOLLOWING ENTRY OF THE PRESENT AMENDMENT". All of the currently pending claims are consolidated in this list for the convenience of the Examiner.

If the Examiner has any questions, she is respectfully requested to contact Applicant's Agent, Ivor M. Hughes or Marcelo K. Sarkis at (905) 771-6414 collect at her convenience.

Respectfully submitted,

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Enclosures

1. Requisition for 3 Month Extension of Time
2. Cheque for $920.00 U.S.
3. Exhibit "A" (marked up claims)
4. Exhibit "B" (clean set of claims)
5. Exhibit "C" (Bodmeier, R. et al. entitled "The Influence of Buffer Species and Strength on Diltiazem HCl Release from Beads Coated with the Aqueous Cationic Polymer Dispersions, Eudragit RS, RL 30D")
6. Exhibit "D" (article of May 17, 2002)

Application Serial No. 09/567,451
Group Art Unit 1615

EXHIBIT A
CLAIMS WITH MARKINGS TO SHOW CHANGES

1. (Twice Amended) A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem selected from the group consisting of Diltiazem and [including] the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg (as desired) of the form of Diltiazem associated with excipients including a neutral copolymer to provide controlled (sustained) release of the form of Diltiazem for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the form of Diltiazem is adapted to be released after administration over a prolonged period of time and exhibits when given to humans

(i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and

(ii) bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria.

2. (Amended) The controlled release Galenical preparation of claim 1 wherein the higher bioavailability achieved after night administration of the preparation than morning administration without food exceeds 25% C_{max}, and the neutral copolymer is a neutral acrylic copolymer of ethyl acrylate and methyl methacrylate.

4. (Twice Amended) The controlled-release Galenical preparation of claim 1 wherein the form of Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 1% and about 15% after 2 hours;

(b) between about 7% and about 35% after 4 hours;

(c) between about 30% and about 58% after 8 hours;

(d) between about 55% and about 80% after 14 hours; and

(e) and in excess of about 75% after 24 hours.

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 1% and about 25% after about 2 hours;

(b) between about 7% and about 45% after about 4 hours;

(c) between about 30% and about 68% after about 8 hours;

(d) in excess of about 75% after about 24 hours.

5. (Twice Amended) The controlled-release Galenical preparation of claim 2 in which the form of Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;

(b) between about 16% and about 21% after 4 hours;

(c) between about 44% and about 52% after 8 hours;

(d) between about 69% and about 76% after 14 hours; and

(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;

(b) between about 16% and about 30% after 4 hours;

(c) between about 44% and about 62% after 8 hours;

(d) in excess of about 80% after 24 hours.

7. (Amended) The preparation of claim 1, 2, 4, 5 or 6 wherein the form of Diltiazem is in the form of Diltiazem HCl.

48. (Twice Amended) The preparation of claim 17 wherein the wetting agent is selected from:

sugars;

saccharose, mannitol, sorbitol;

lecithins;

C_{12} to C_{20} fatty acid esters of saccarose[, including sucrose stearate];

xylose esters or xylites;

polyoxyethylenic glycerrides;

esters of fatty acids and polyoxyethylene;

sorbitan fatty acid ester;

polyglycides-glycerides and polyglycides-alcohols esters

Metal salts.

52. (Third Amendment) A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem selected from the group consisting of Diltiazem and [including] the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg (as

desired) of the form of Diltiazem associated with excipients to provide controlled (sustained) release of the form of Diltiazem for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the form of Diltiazem is adapted to be released after administration over a prolonged period of time and exhibits when given to humans

(i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and

(ii) bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose [(Avicel ph101)]	8 - 9.5
(c)	[Povidone K30] (Polyvinyl Pyrrolidone)	1 - 2
(d)	Sucrose stearate	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	[Polysorbate 80 (tween)] (Polyoxyethylene Sorbitan Monooleate)	0.01 - 0.025
(j)	Simethicone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester	

(dry of 30%)	7 - 11
Purified water USP	0 (used for mixing)

64. (Third Amendment) A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem selected from the group consisting of Diltiazem and [including] the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg (as desired) of the form of Diltiazem associated with excipients to provide controlled (sustained) release of the form of Diltiazem for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the form of Diltiazem is adapted to be released after administration over a prolonged period of time and exhibits when given to humans

(i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and

(ii) bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria, in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and.

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants,

wherein the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose [(Avicel ph101)]	8 - 9.5
(c)	[Povidone K30] (Polyvinyl Pyrrolidone)	1 - 2
(d)	Sucrose stearate [(crodesta F150)]	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	[Polysorbate 80 (tween)] (Polyoxyethylene Sorbitan Monooleate)	0.01 - 0.025

(j)	Simethicone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing).

110. (Twice Amended) A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem selected from the group consisting of Diltiazem and [including] the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;

(b) between about 16% and about 21% after 4 hours;

(c) between about 44% and about 52% after 8 hours;

(d) between about 69% and about 76% after 14 hours; and

(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;

(b) between about 16% and about 30% after 4 hours;

(c) between about 44% and about 62% after 8 hours;

(d) in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the wetting agent is selected from:

sugars;

saccharose, mannitol, sorbitol;

lecithins;

C_{12} to C_{20} fatty acid esters of saccarose[, commercialized under the name of sucroesters or under the name of crodesters such as sucrose stearate marketed under the trade name of Crodesta];

xylose esters or xylites;

polyoxyethylenic glycerrides;

esters of fatty acids and polyoxyethylene;

sorbitan fatty acid esters;

polyglycides-glycerides and polyglycides-alcohols esters

Metal salts.

114. (Third Amendment) A controlled-release Galenical preparation of pharmaceutically acceptable <u>form of</u> Diltiazem <u>selected from the group consisting of Diltiazem and</u> [including] the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is

adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;

(b) between about 16% and about 21% after 4 hours;

(c) between about 44% and about 52% after 8 hours;

(d) between about 69% and about 76% after 14 hours; and

(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;

(b) between about 16% and about 30% after 4 hours;

(c) between about 44% and about 62% after 8 hours;

(d) in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, in which the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose	8 - 9.5
(c)	[Povidone K30] (Polyvinyl Pyrrolidone)	1 - 2
(d)	Sucrose stearate	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5

(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	[Polysorbate 80 (tween)] (Polyoxyethylene Sorbitan Monooleate)	0.01 - 0.025
(j)	Simethicone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing)

116. (Twice Amended) A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem selected from the group consisting of Diltiazem and [including] the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;

(b) between about 16% and about 21% after 4 hours;

(c) between about 44% and about 52% after 8 hours;

(d) between about 69% and about 76% after 14 hours; and

(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;

(b) between about 16% and about 30% after 4 hours;

(c) between about 44% and about 62% after 8 hours;

(d) in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

118. (Twice Amended) A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem selected from Diltiazem and [including] the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;

(b) between about 16% and about 21% after 4 hours;

(c) between about 44% and about 52% after 8 hours;

(d) between about 69% and about 76% after 14 hours; and

(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;

(b) between about 16% and about 30% after 4 hours;

(c) between about 44% and about 62% after 8 hours;

(d) in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, in which the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

122. (Twice Amended) A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem selected from the group consisting of Diltiazem and [including] the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

126. (Twice Amended) The preparation of claim 122, 123 or 124 wherein the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose [(Avicel ph101)]	8 - 9.5
(c)	[Povidone K30] (Polyvinyl Pyrrolidone)	1 - 2
(d)	Sucrose stearate [(crodesta F150)]	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	[Polysorbate 80 (tween)] (Polyoxyethylene Sorbitan Monooleate)	0.01 - 0.025
(j)	Simethicone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	[Eudragit NE30 D] <u>a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester</u> (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing).

Application Serial No. 09/567,451
Group Art Unit 1615

EXHIBIT B
CLEAN SET OF ALL PENDING CLAIMS FOLLOWING ENTRY OF THE PRESENT AMENDMENT

1. A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem selected from the group consisting of Diltiazem and the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg (as desired) of the form of Diltiazem associated with excipients including a neutral copolymer to provide controlled (sustained) release of the form of Diltiazem for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the form of Diltiazem is adapted to be released after administration over a prolonged period of time and exhibits when given to humans

(i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and

(ii) bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria.

2. The controlled release Galenical preparation of claim 1 wherein the higher bioavailability achieved after night administration of the preparation than morning administration without food exceeds 25% C_{max}, and the neutral copolymer is a neutral acrylic copolymer of ethyl acrylate and methyl methacrylate.

3. A method of treatment of a patient's hypertension and/or angina comprising administration of a preparation of claim 1 in the night to a patient for effect the next morning and which formulation exhibits a higher bioavailability when given at night compared to when given in the morning without food according to FDA

guidelines or criteria and bioequivalence when given with food and without food according to the same FDA guidelines or criteria.

4. The controlled-release Galenical preparation of claim 1 wherein the form of Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 1% and about 15% after 2 hours;

(b) between about 7% and about 35% after 4 hours;

(c) between about 30% and about 58% after 8 hours;

(d) between about 55% and about 80% after 14 hours; and

(e) and in excess of about 75% after 24 hours.

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 1% and about 25% after about 2 hours;

(b) between about 7% and about 45% after about 4 hours;

(c) between about 30% and about 68% after about 8 hours;

(d) in excess of about 75% after about 24 hours.

5. The controlled-release Galenical preparation of claim 2 in which the form of Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;

(b) between about 16% and about 21% after 4 hours;

(c) between about 44% and about 52% after 8 hours;

(d) between about 69% and about 76% after 14 hours; and

(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;

(b) between about 16% and about 30% after 4 hours;

(c) between about 44% and about 62% after 8 hours;

(d) in excess of about 80% after 24 hours.

6. The preparation of claim 4 wherein the Cmax of Diltiazem in the blood is obtained between about 11 - about 13 hours after administration of the preparation.

7. The preparation of claim 1, 2, 4, 5 or 6 wherein the form of Diltiazem is in the form of Diltiazem HCl.

8. The preparation of claim 6 wherein the preparation is a diffusion controlled preparation.

9. The preparation of claim 5 wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution.

10. The preparation of claim 9 in capsule form.

11. The preparation of claim 9 in tablet form.

12. The preparation of claim 9 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.

13. The preparation of claim 12 wherein the Diltiazem is mixed (in whole or in part) with the wetting agent.

14. The preparation of claim 13 wherein the wetting agent assists to maintain the solubility of the Diltiazem in each microgranule, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.

15. The preparation of claim 14 wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

16. The preparation of claim 12 wherein the preparation comprises a mixture of the Diltiazem and/or pharmaceutically acceptable salt with the wetting agent and the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

17. The preparation of claim 16 wherein the membrane comprises a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester and hydroxypropylmethylcellulose.

18. The preparation of claim 17 wherein the membrane hydrates the core within a membrane which when put in gastrointestinal fluid causes the membrane to swell

while fluid penetrates and hydrates the microgranule, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).

19. The preparation of claim 13 wherein the Diltiazem is mixed with the wetting agent and the membrane comprises an acrylic membrane and plasticizer combined to form the membrane thereby providing a mechanism of release from this membrane which "washes" the diltiazem through pores created when the plasticizer incorporated in the membrane, is released in gastrointestinal fluid.

20. The preparation of claim 9 wherein the preparation comprises a plurality of microgranules comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or a pharmaceutically acceptable salt thereof associated with any suitable dissolution agent (other than a wetting agent) to assist in the release of the Diltiazem from the preparation.

21. The preparation of claim 20 wherein the dissolution agent is an organic acid comprising adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid or tartaric acid which permits the diltiazem to dissolve in gastrointestinal fluids even when the microgranules pass into the regions of the gastrointestinal tract of the intestine at which pH diltiazem is much less soluble.

22. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 1 or 2 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

23. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 4 to the patient in the

evening for effective treatment of the patient's hypertension and/or angina the next morning.

24. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 5 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

25. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 6 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

26. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 7 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

27. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 8 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

28. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 9 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

29. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 10 to the patient in the

evening for effective treatment of the patient's hypertension and/or angina the next morning.

30. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 11 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

31. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 12 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

32. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 13 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

33. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 14 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

34. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 15 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

35. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 16 to the patient in the

evening for effective treatment of the patient's hypertension and/or angina the next morning.

36. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 17 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

37. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 18 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

38. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 19 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

39. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 20 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

40. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 21 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

41. The preparation of claim 5 wherein the preparation contains 120 mg of Diltiazem.

42. The preparation of claim 5 wherein the preparation contains 180 mg of Diltiazem.

43. The preparation of claim 5 wherein the preparation contains 240 mg of Diltiazem.

44. The preparation of claim 5 wherein the preparation contains 300 mg of Diltiazem.

45. The preparation of claim 5 wherein the preparation contains 360 mg of Diltiazem.

46. The preparation of claim 5 wherein the preparation contains 420 mg of Diltiazem.

47. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 41, 42, 43, 44, 45 or 46 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

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48. The preparation of claim 17 wherein the wetting agent is selected from:

sugars;
saccharose, mannitol, sorbitol;
lecithins;
C_{12} to C_{20} fatty acid esters of saccarose;
xylose esters or xylites;
polyoxyethylenic glycerrides;
esters of fatty acids and polyoxyethylene;
sorbitan fatty acid ester;

Cf cont

polyglycides-glycerides and polyglycides-alcohols esters

Metal salts.

49. The preparation of claim 12 wherein the wetting agent is in association with the diltiazem in the microgranule and not mixed therewith, the membrane comprises a water-soluble or water dispersible polymer or copolymer such as hydroxypropylmethylcellulose and a water-, acid- and base-insoluble polymer which is a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester enabling the bead to be hydrated by the introduction of intestinal fluids into the core hydrating the core and therefore mixing the diltiazem and the wetting agent.

50. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 48 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

51. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 49 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

52. A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem selected from the group consisting of Diltiazem and the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg (as desired) of the form of Diltiazem associated with excipients to provide controlled (sustained) release of the form of Diltiazem for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the form of Diltiazem is

adapted to be released after administration over a prolonged period of time and exhibits when given to humans

(i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and

(ii) bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose	8 - 9.5
(c)	(Polyvinyl Pyrrolidone)	1 - 2
(d)	Sucrose stearate	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	(Polyoxyethylene Sorbitan Monooleate)	0.01 - 0.025
(j)	Simethicone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing)

cont

53. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 48 to the patient in the

evening for effective treatment of the patient's hypertension and/or angina the next morning.

54. The preparation of claim 12 in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

55. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 54 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

56. .The preparation of claim 12 in which the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

57. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 56 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

58. The preparation of claim 12 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with suitable excipients and adjuvants.

59. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 58 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

60. The controlled-release Galenical preparation of claim 2 in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

61. The preparation of claim 60 wherein the microgranules are in capsule form.

62. The preparation of claim 60 wherein the microgranules are in tablet form.

63. The preparation of claim 60 wherein the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

64. A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem selected from the group consisting of Diltiazem and the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg (as desired) of the form of Diltiazem associated with excipients to provide controlled (sustained) release of the form of Diltiazem for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the form of Diltiazem is adapted to be released after administration over a prolonged period of time and exhibits when given to humans

(i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and

(ii) bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria, in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants,

wherein the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose	8 - 9.5
(c)	(Polyvinyl Pyrrolidone)	1 - 2
(d)	Sucrose stearate	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	(Polyoxyethylene Sorbitan Monooleate)	0.01 - 0.025
(j)	Simethicone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11

C4 cont

Purified water USP	0 (used for mixing).

65. The preparation of claim 60 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with suitable excipients and adjuvants.

66. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 60 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

110. A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem selected from the group consisting of Diltiazem and the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

C7

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;

(b) between about 16% and about 21% after 4 hours;

(c) between about 44% and about 52% after 8 hours;

(d) between about 69% and about 76% after 14 hours; and

(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;

(b) between about 16% and about 30% after 4 hours;

(c) between about 44% and about 62% after 8 hours;

(d) in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the wetting agent is selected from:

sugars;

saccharose, mannitol, sorbitol;

lecithins;

C_{12} to C_{20} fatty acid esters of saccarose;

xylose esters or xylites;

polyoxyethylenic glycerrides;

esters of fatty acids and polyoxyethylene;

sorbitan fatty acid esters;

polyglycides-glycerides and polyglycides-alcohols esters

Metal salts.

C7 cont

112. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 110 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

113. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 111 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

114. A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem selected from the group consisting of Diltiazem and the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;

(b) between about 16% and about 21% after 4 hours;

(c) between about 44% and about 52% after 8 hours;

(d) between about 69% and about 76% after 14 hours; and

(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;

(b) between about 16% and about 30% after 4 hours;

(c) between about 44% and about 62% after 8 hours;

(d) in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, in which the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose	8 - 9.5
(c)	(Polyvinyl Pyrrolidone)	1 - 2
(d)	Sucrose stearate	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	(Polyoxyethylene Sorbitan Monooleate)	0.01 - 0.025
(j)	Simethicone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing)

115. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 112 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

116. A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem selected from the group consisting of Diltiazem and the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;

(b) between about 16% and about 21% after 4 hours;

(c) between about 44% and about 52% after 8 hours;

(d) between about 69% and about 76% after 14 hours; and

(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;

(b) between about 16% and about 30% after 4 hours;

(c) between about 44% and about 62% after 8 hours;

(d) in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the

central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

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117. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 116 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

118. A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem selected from Diltiazem and the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;

(b) between about 16% and about 21% after 4 hours;

(c) between about 44% and about 52% after 8 hours;

(d) between about 69% and about 76% after 14 hours; and

(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;

(b) between about 16% and about 30% after 4 hours;

(c) between about 44% and about 62% after 8 hours;

(d) in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, in which the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

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119. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 118 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

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122. A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem selected from the group consisting of Diltiazem and the

CII

pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

123. The preparation of claim 122 wherein the microgranules are in capsule form.

124. The preparation of claim 122 wherein the microgranules are in tablet form.

125. The preparation of claim 122, 123 or 124 wherein the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

126. The preparation of claim 122, 123 or 124 wherein the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose	8 - 9.5
(c)	(Polyvinyl Pyrrolidone)	1 - 2
(d)	Sucrose stearate	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	(Polyoxyethylene Sorbitan Monooleate)	0.01 - 0.025
(j)	Simethicone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing).

127. The preparation of claim 122 or 124 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with suitable excipients and adjuvants.

128. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 122, 123 or 124 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Exhibit "C"

Pharmaceutical Research, Vol. 13, No. 1, 1996 *Report*

The Influence of Buffer Species and Strength on Diltiazem HCl Release from Beads Coated with the Aqueous Cationic Polymer Dispersions, Eudragit RS, RL 30D

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Received June 19, 1995; accepted September 29, 1995

Purpose. Eudragit RL and RS 30D are pseudolatexes frequently used in the coating of solid dosage forms. They are based on cationic copolymers stabilized with quaternary ammonium groups (poly(ethylacrylate-methylmethacrylate-trimethylammonioethyl methacrylate chloride). A pH-independent drug release is expected because of the quaternary nature of the cationic groups. The objective was to explain a distinct "pH-dependent" drug release in various buffer media with coated diltiazem beads.

Methods. The diltiazem HCl release from and water uptake of Eudragit RS/RL-coated beads was determined in various buffers of different buffer species, pH or concentration.

Results. The drug release in the different buffer media was in the following order: pH 5.0 acetate > pH 3.5 formate > pH 7.4 phosphate buffer > 0.1M HCl). This "pH-dependent" drug release could be explained with an anion exchange process; the chloride counterions of the quaternary groups were exchanged with the anionic buffer species during the dissolution study. The water uptake of the coated beads correlated well with the drug release from the beads. Increasing the buffer strength (acetate buffer) first increased and then decreased the drug release, while increasing the ionic strength of different buffers with NaCl decreased the drug release and eliminated the observed buffer effects because of the excess of chloride ions.

Conclusions. The anionic buffer species and not the pH had a significant effect on the hydration and hence on the drug release from beads coated with the cationic polymers, Eudragit RS and RL.

KEY WORDS: beads; buffer species; coating; drug release; latex; Eudragit RS 30D.

INTRODUCTION

Acrylic, water-insoluble polymers have been used extensively to develop oral controlled release drug delivery systems in the form of coated particles, beads or tablets (1-3). These polymers are applied either in the form of organic solutions or as aqueous colloidal dispersions. Eudragit RL and RS 30D are pseudolatexes of poly(ethylacrylate-methylmethacrylate-trimethylammonioethyl methacrylate chloride) copolymers with ratios of 1:2:0.2 and 1:2:0.1 with a polymer content of 30% w/v. The colloidal polymer particles are stabilized in water by the positively charged quaternary ammonium groups present in the polymer. These quaternary ammonium groups are in the chloride salt form. Films or coatings prepared from Eudragit RS or RL 30D are insoluble in aqueous media over the physiological pH-range, however, they swell and hydrate and are permeable to drugs because of the presence of the ionized quaternary ammonium groups.

The permeability of these films and the drug release from coated dosage forms has been described to be pH-independent (4,5). Due to the quaternary groups, the degree of ionization of the polymer should not be affected by pH within the physiological pH range. In this study, surprisingly, a pH-dependent drug release was observed from diltiazem HCl beads coated with Eudragit RS/RL 30D. The solubility of diltiazem HCl was fairly independent of the pH in the investigated pH-range and was not responsible for the observed pH-dependency. The "pH-dependent" release was therefore caused by the polymeric coating.

In a preliminary study, it was shown that the aqueous buffer medium had a significant influence on the hydration and the time-dependent wet mechanical properties of polymeric films prepared from Eudragit RS 30D (6). It was suggested, that the anionic buffer species replaced the chloride-counterions of the quaternary ammonium groups of the polymer during the hydration study and therefore affected the rate and extent of hydration.

The objective of this study was to explain the observed "pH-dependent" drug release from beads coated with the cationic polymers, Eudragit RS/RL. The effect of pH, buffer species, buffer strength and ionic strength on the drug release from the coated beads and the relationship between polymer hydration and drug release were investigated.

MATERIALS AND METHODS

Materials

The following chemicals were obtained from commercial suppliers and used as received: Eudragit RL and RS 30D [poly(ethylacrylate-methylmethacrylate-trimethylammonioethyl methacrylate chloride) copolymers with ratios of 1:2:0.2 and 1:2:0.1] (Röhm, Darmstadt, Germany); acetyl tributyl citrate (ATBC) (Morflex, Inc., Greensboro, North Carolina); sodium phosphate, dibasic; potassium phosphate, monobasic; hydrochloric acid and citric acid, anhydrous (Fisher, Fair Lawn, New Jersey); sodium hydroxide and formic acid, 90% (J.T. Baker, Phillipsburg, NJ); acetic acid, glacial (Mallinckrodt, Paris, Kentucky). Diltiazem HCl powder and diltiazem HCl coated beads were obtained from Marion Merrell Dow (Kansas City, Missouri).

Dissolution and Hydration Media

The following aqueous dissolution media were used: pH 1.0 (0.1 M HCl), pH 3.5 (formic acid-NaOH), pH 5.0 (acetic acid-NaOH) and pH 7.4 (sodium phosphate, dibasic - potassium phosphate, monobasic). The ionic strength of the four

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buffers was kept the same by adding calculated amounts of buffer species (7). The McIlvaines' buffer (citric acid - sodium phosphate, dibasic) was selected to cover a wide pH-range with the same buffer species; the total ionic strength of the buffered solution was adjusted to 0.5 M with NaCl.

Solubility of Diltiazem HCl

Excess amount of diltiazem HCl was placed in the desired buffer medium. The samples were shaken for 48 hours at 37 °C. The saturated drug solutions were filtered and then assayed spectrophotometrically at 236 nm after appropriate dilution (n=3). The final pH of the saturated solution was recorded. The drug solubilities were similar in pH 3.5 formate buffer (652 mg/ml, final pH = 3.46), pH 5.0 acetate buffer (678 mg/ml, final pH = 4.87) and pH 7.4 phosphate buffer (634 mg/ml, final pH = 5.82); the drug solubility in 0.1M HCl was 588 mg/ml. The lower drug solubility in 0.1M HCl solution was probably caused by the common ion effect of the chloride-ion (8).

Dissolution Studies

The USP XXI rotating paddle method (0.2 g beads, 37 °C, 50 rpm, 900 ml medium, n=3, coefficient of variation <5%, dissolution apparatus from Hanson Research Corp., Northridge, California) was used to investigate the drug release from beads coated with Eudragit RS/RL 30D. At predetermined time intervals, samples (2 ml) were withdrawn and replaced with fresh medium. The drug solution was assayed spectrophotometrically either directly or after dilution with the release medium at 236 nm. The residual drug content of the beads after the dissolution study was determined spectrophotometrically after completely crushing the beads with a glass rod. The amount of drug released and the residual drug content in the beads matched the original drug content closely (99.6-104.4%). The release rate and lag time were obtained by a linear regression method from the linear part of the release curve.

Water Uptake of the Coated Beads

At predetermined time intervals, beads (approximately 1 g, accurately weighed) were taken from the release medium with a 60 mesh sieve (the conditions for the water uptake studies were the same as with the dissolution study). The beads were immediately washed twice with distilled water (100 ml) in order to remove the buffer solution from the surface of the beads and were then blotted with lint-free tissue paper. The weight of the beads was recorded before and after drying to constant weight in an oven at 50 °C. The water uptake was calculated as follows: water uptake = W(t) - W (d) / W(d), where W(t) is the weight of the wet beads removed at time t and W(d) is the weight of the beads after drying at time t. The water uptake data are represented as g water / g bead (n=3, coefficient of variation <6%).

RESULTS AND DISCUSSION

In this study, the unexpected "pH-dependent" drug release from diltiazem HCl beads coated with the acrylic polymer dispersions, Eudragit RS and RL 30D, was investigated. Although the drug release has been described to be pH-independent (4, 5), a distinct pH-dependency of the diltiazem HCl release from coated beads was observed (Figure 1). The drug release was determined in media of different pH and of different buffer species (pH 1.0 - hydrochloric acid, pH 3.5 - formic acid-NaOH, pH 5.0 -acetic acid-NaOH and pH 7.4 -sodium phosphate, dibasic-potassium phosphate, monobasic) at a buffer strength of 0.1 M.

The solubility of diltiazem HCl was fairly independent of the pH and could be excluded as the reason for the pH-dependent drug release. The pH-dependent release was therefore caused by the cationic polymeric coating. The drug release profiles had a sigmoidal shape with three phases. A lag phase with little drug release was followed by a rapid, linear release phase followed again by a slow release phase. Especially the extent of the lag time and the rapid release phase were strongly affected by the buffer medium. The drug release was fastest and the lag time shortest with acetate buffer (pH 5.0) followed by formate buffer (pH 3.5), phosphate buffer (pH 7.4) and hydrochloric acid (pH 1.0).

In order to explain the observed "pH-dependent" drug release behaviour, emphasis should be shifted from pH-considerations to the influence of the anionic buffer species present in the dissolution media. An ion exchange mechanism can be used to explain the drug release from the coated beads. Eudragit RS and RL contain 33 and 66 mole of quaternary ammonium groups per mole of polymer (9). The dissociation of these quaternary ammonium groups in aqueous media is responsible for the hydration and swelling of the polymer coating or films. The anionic counterions of the quaternary ammonium groups are chloride ions. With ion exchange resins, ions are bound to an insoluble crosslinked polymer resin carrying oppositely charged functional groups such as quaternary ammonium groups. The affinity of ions to ion exchange resins is characterized by the ion selectivity coefficient. Accordingly, the degree of hydration and swelling of the resins is affected by this interaction (10, 11). Applying this concept to the present study, the chloride counterions of the quaternary ammonium groups in Eudragit RS/RL could be replaced by the buffer anions of the dissolution medium during dissolution studies. The degree of hydration and swelling and subsequently the drug release was governed by the interaction between the cationic groups and the counterions.

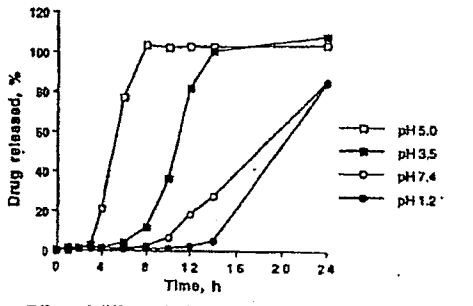

Fig. 1. Effect of different buffers (0.1 M) on the diltiazem HCl release from Eudragit RS/RL 30D coated beads (pH 1.0 - hydrochloric acid; pH 3.5 - formate buffer; pH 5.0 - acetate buffer; pH 7.4 - phosphate buffer).

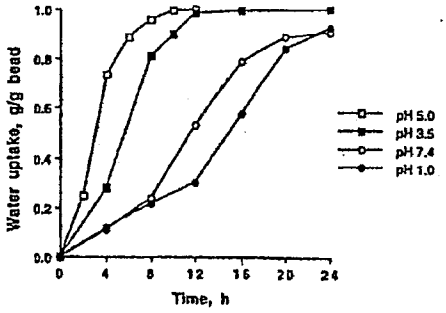

Fig. 2. Effect of different buffers (0.1 M) on the water uptake of Eudragit RS/RL 30D coated beads (pH 1.0 - hydrochloric acid; pH 3.5 - formate buffer; pH 5.0 - acetate buffer; pH 7.4 - phosphate buffer).

The selectivity coefficients of the buffer anions for anion exchangers are in the following order: chloride > formate > acetate (10, 11). A larger selectivity coefficient indicates a stronger interaction between the fixed groups and the counterions and therefore a lesser degree of hydration or swelling; a slower drug release is expected. The order of the selectivity coefficients agreed with the results shown in Figure 1; the order in the drug release (acetate > formate > chloride) was inverse to the order of the selectivity coefficients.

The diffusion of the dissolution medium through and the hydration of the cationic, acrylic polymer coating precedes the drug release through the hydrated polymer film. In order to characterize this hydration phase as a function of pH (buffer species), the water uptake of the beads as a function of time was determined. As shown in Figure 2, the water uptake correlated well with the drug release. The water uptake (swelling) of the Eudragit RS/RL coatings was also in the reverse order of the selectivity coefficients.

The diltiazem HCl release profile and two parameters characterizing the release curve, the release rate and the lag time, as a function of buffer strength (0.01 - 0.5 M, pH 5.0 acetate buffer) are shown in Figures 3 and 4. The drug release rate initially increased with increasing buffer strength and then decreased at higher buffer strength; as expected, the opposite pattern was observed with the lag time. A possible explanation could be as follows. At low buffer strength

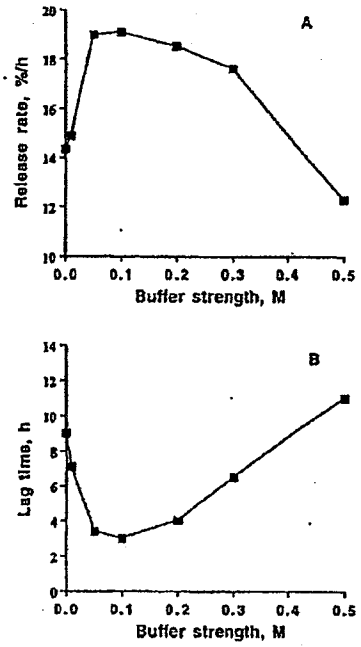

Fig. 4. Effect of buffer strength (pH 5.0 acetate buffer) on the release rate and lag time of the diltiazem HCl release from Eudragit RS/RL 30D coated beads. A: release rate, B: lag time.

(0.01 M), not enough acetate ions were present to replace the original chloride ions. The degree of hydration was therefore governed primarily by the chloride salt form of the polymer, thus explaining the slower drug release. Increasing the acetate concentration resulted in the exchange of the chloride with the acetate ions and therefore in a faster drug release and shorter lag times. The reduction in drug release at high buffer strength could be explained with the high osmotic pressure of the dissolution medium. Again, the water uptake and the rate of water uptake correlated well with the release data (Figures 5 and 6).

Sodium chloride is often added to adjust the ionic

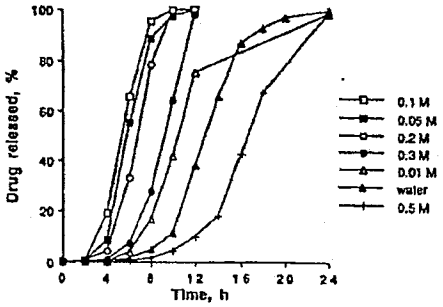

Fig. 3. Effect of buffer strength (pH 5.0 acetate buffer) on the diltiazem HCl release from Eudragit RS/RL 30D coated beads.

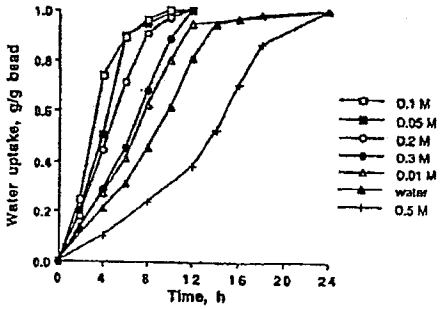

Fig. 5. Effect of buffer strength (pH 5.0 acetate buffer) on the water uptake of diltiazem HCl beads coated with Eudragit RS/RL 30D.

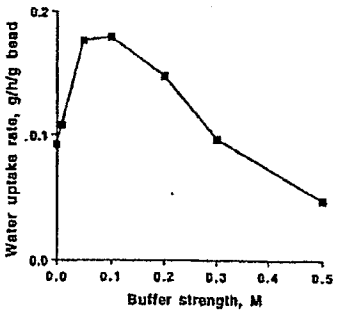

Fig. 6. Effect of buffer strength (pH 5.0 acetate buffer) on the water uptake rate of diltiazem HCl beads coated with Eudragit RS/RL 30D.

strength of different buffer media to the same value. The influence of the addition of NaCl (0.1, 0.4, 0.9 M) to three buffers of the same buffer strength (0.1 M; pH 1.0 - hydrochloric acid, pH 3.5 formate buffer, pH 7.4 - phosphate buffer) was investigated (Figure 7). Without NaCl-addition, the drug release in pH 3.5 buffer was much faster than in pH 1 or pH 7.4 buffers (Figure 7A). However, upon adding NaCl, the differences in the drug release patterns disappeared and the release curves for the three media were almost identical (Figure 7 B-D). The additional chloride counterions in the medium "overpowered" the acetate ions and controlled the hydration and hence the drug release from the beads. As expected the drug release decreased with increasing ionic strength of the dissolution medium. This could be attributed to the lower solubility of the drug (8) and to the higher osmotic pressure of the dissolution medium which decreased the water uptake of the polymer.

The drug release from the coated beads was then tested

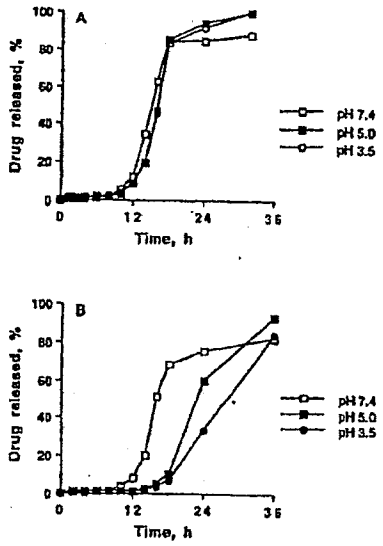

Fig. 8. Effect of pH on the diltiazem HCl release from Eudragit RS/RL 30D coated beads in McIlvaine's buffer. A: at different ionic strength: pH 3.5 - μ=0.13; pH 5.0 - μ=0.25; pH 7.4 - μ=0.46, B: same ionic strength, adjusted to 0.5 M by adding NaCl.

in buffers having different pH values but containing the same buffer species (citrate-phosphate) in varying ratios (McIlvaine's buffer) (Figure 8). The ionic strength of the buffer system at different pH values (pH 3.5, pH 5.0 and pH 7.4), however, was different. The drug release patterns were almost superimposible in buffers having the same type of buffer species but different ionic strengths (0.13 M for pH

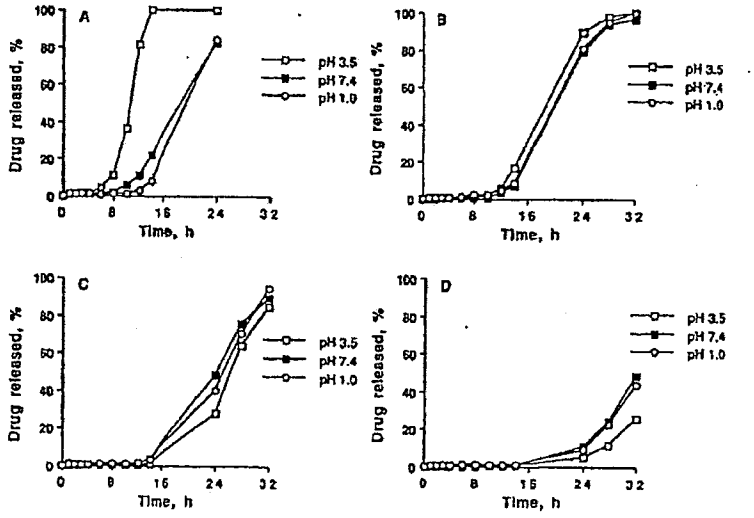

Fig. 7. Effect of NaCl addition to buffers of different pH (0.1M) on the diltiazem HCl release from Eudragit RS/RL 30D coated beads. A: no NaCl, B: 0.1 M NaCl, C: 0.4 M NaCl, D: 0.9 M NaCl.

3.5, 0.25 for pH 5.0 and 0.46 for pH 7.4) (Figure 8 A). In contrast, differences in drug release were observed after adjusting the buffers to the same ionic strength ($\mu = 0.5$ M) with NaCl (26) (Figure 8 B). The drug release was fastest in pH 7.4, followed by pH 5.0 and then pH 3.5, this order being opposite to the amount of NaCl added to adjust to the same ionic strength. As explained above, increasing the amount of NaCl decreased the hydration of the polymeric film and the drug solubility and therefore the drug release.

In conclusion, the anionic buffer species and not the pH had a significant effect on the hydration and hence on the drug release from beads coated with the cationic polymers, Eudragit RS and RL. The buffer-dependent release data could be explained with the ion exchange of the chloride counterions of the polymer with the anionic buffer species during dissolution studies.

ACKNOWLEDGMENTS

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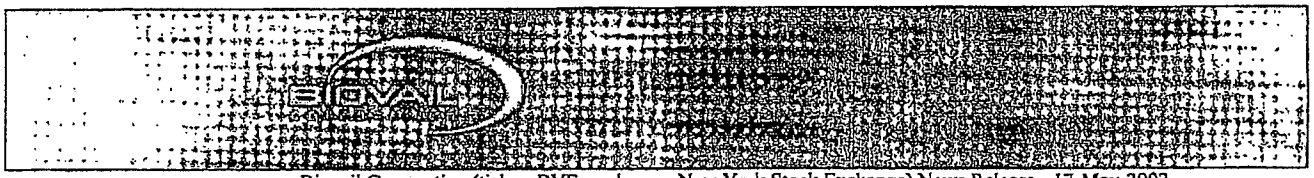
Exhibit "D"



Biovail Corporation (ticker: BVF, exchange: New York Stock Exchange) News Release - 17-May-2002

Biovail Reports New Graded-Release Diltiazem Helps Control Blood Pressure Surges

OVERVIEW
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NEW YORK--(BW HealthWire)--May 17, 2002--

Results Presented at ASH Show Novel Therapy Synchronizes with

Natural Body Rhythms to Maximize Protection

Biovail Corporation (NYSE:BVF - News; TSE:BVF - News) today announced a new graded-release formulation of diltiazem hydrochloride dosed at 10 p.m. provided the most significant reductions in blood pressure in the hours between 6 a.m. and noon, a time when risk of heart attack and stroke is greatest. The formulation is currently under investigation as an antihypertensive therapy.

According to researchers presenting at the 17th Annual Scientific Meeting of the American Society of Hypertension, a 360 mg nighttime dose of graded-release diltiazem lowered both diastolic and systolic blood pressure readings significantly more during the high-risk hours than an identical dose administered in the morning. In addition, single nighttime doses of varying strengths were all shown to provide clinically important antihypertensive effects around the clock.

"Morning surges in blood pressure pose real risks to people with cardiovascular disease, yet most are treated with traditional therapies that do little to address these potentially dangerous peaks," said Stephen Glasser, MD, lead study author and professor of epidemiology at the University of Minnesota, School of Public Health. "Our investigational study demonstrates that graded-release diltiazem dosed in the evening delivers maximum antihypertensive effects in the morning hours when patients need it most."

Graded-release diltiazem is being evaluated as chronotherapy, or treatment synchronized to the body's natural rhythms, known as circadian rhythms. Blood pressure is highly sensitive to circadian variations and follows a predictable cycle, including a substantial rise upon early-morning awakening, a plateau during daily activities and a decline of approximately 20 percent during sleep. The early-morning surge is particularly concerning to clinicians and may be an important factor in the increased incidence of life-threatening cardiovascular events in the period from 6 a.m. to noon. Data show a 40 percent higher risk of heart attack, a 29 percent higher risk of cardiac death and a 49 percent higher risk of stroke during these critical morning hours.(1)

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Glasser and colleagues compared the safety and efficacy of graded-release diltiazem at once-daily nighttime (10 p.m.) doses of 120 mg, 240 mg, 360 mg and 540 mg with placebo. In a separate study arm, they compared a 360 mg nighttime dose with an equal dose administered in the morning (8 a.m.). The study involved 478 adult patients with moderate-to-severe high blood pressure.

Results showed that all nighttime doses of graded-release diltiazem produced dose-related reductions in trough diastolic and systolic blood pressure (6 p.m. to 10 p.m.), demonstrating that the agent maintains its antihypertensive effect for a complete 24-hour period.

Researchers highlighted data showing the 360 mg nighttime dose lowered mean diastolic blood pressure (DBP) between 6 a.m. and noon by an additional 3.3 millimeters of mercury (mmHg) and mean systolic blood pressure (SBP) by an additional 5.3 mmHg when compared with the equivalent morning dose. Lowering mean SBP is especially significant since recent data show SBP may be a better predictor than DBP of coronary artery disease, heart failure, stroke and death.(2)

"The improved efficacy of the evening dose during the high-risk morning hours demonstrates the ability of this new formulation to synchronize with circadian rhythms," said Glasser. "Our findings reinforce that nighttime dosing of chronotherapeutic agents is an important option to maximize blood pressure control when patients are at greatest risk for cardiovascular events."

Study data also showed the 540 mg dose, when administered at night, was well tolerated and demonstrated optimal mean blood pressure reductions from 6 a.m. to noon (14.8 mmHg DBP and 18.5 mmHg SBP), suggesting it may serve as a further therapeutic option when more aggressive treatment is desired.

Discontinuation due to adverse events was higher in the placebo group (4.3%) than in the diltiazem group (3.2%). Treatment-related side effects were statistically similar between patients who received graded-release diltiazem (14.2%) and those in the placebo group (13%).

The most commonly reported treatment-related side effects in the diltiazem group were lower limb edema (4.2%) and headache (3.9%).

In a separate meeting, Biovail also disclosed its plans for additional Phase IV clinical trials for graded-release diltiazem. The studies will compare the chronotherapeutic benefits of the product versus Norvasc(R) (amlodipine besylate) and Altace(R) (ramipril). Study populations will include diabetic hypertensives, African-American hypertensives and Stage I and II hypertensive patients. It is anticipated that initial results on two of these studies will be available by year end.

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To the extent any statements made in this release contain information that is not historical, these statements are essentially forward looking and are subject to risks and uncertainties, including the difficulty of predicting FDA approvals, acceptance and demand for new pharmaceutical products, the impact of competitive products and pricing, new product development and launch, reliance on key strategic alliances, availability of raw materials, the regulatory environment, fluctuations in operating results and other risks detailed from time to time in the company's filings with the Securities and Exchange Commission. ----------

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Norvasc is a registered trademark of Pfizer. Altace is a registered trademark of Monarch Pharmaceuticals.

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